PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY
(PCT Rule 43*bis*.1)

Date of mailing *(day/month/year)* see form PCT/ISA/210 (second sheet)	
Applicant's or agent's file reference see form PCT/ISA/220	**FOR FURTHER ACTION** See paragraph 2 below
International application No. PCT/EP2005/051054	International filing date *(day/month/year)* 09.03.2005
Priority date *(day/month/year)* 10.03.2004	
International Patent Classification (IPC) or both national classification and IPC C07D221/12, A61K31/473, C07D401/12, C07D471/04	
Applicant ALTANA PHARMA AG	

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

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Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☐ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☐ in written format

   ☐ in computer readable form

   c. time of filing/furnishing:

   ☐ contained in the international application as filed.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 17 and 18 (as regards industrial applicability)

because:

☒ the said international application, or the said claims Nos. 17 and 18 relate to the following subject matter which does not require an international preliminary examination *(specify)*:

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the whole application or for said claims Nos.

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-18
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-4, 11-18
	No:	Claims	5-10
Industrial applicability (IA)	Yes:	Claims	1-16
	No:	Claims	

2. Citations and explanations

see separate sheet

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (SEPARATE SHEET)

International application No.

PCT/EP2005/051054

Re Item III.

The present **claims 17** and **18** relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT.
Consequently, no opinion will be formulated with respect to industrial applicability of the subject-matter of these claims.

[For the assessment of the aforesaid claims on the question whether they are industrially applicable, no unified criteria exist in the PCT. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but will allow, however, claims to a (known) *compound for* first *use in medical treatment* and the *use* of such a compound *for the manufacture of a medicament* for a new medical treatment.]

Re Item V.

The following documents (D) are considered to be relevant:

D1: ..... WO-A-97/28131 (7 August 1997);
D2: ..... WO-A-99/05113 (4 February 1999);
D3: ..... WO-A-2004/019944 (***11 March 2004***);

1. NOVELTY (Article 33(2) PCT):

The present application satisfies the criterion set forth in Article 33(2) PCT because the subject-matter of **claims 1-18** is new in respect of prior art as defined in the regulations (Rule 64(1)-(3) PCT):

The compounds of present **claim 1** are novel over the prior art **D1** and **D2** on account of the *oxy substituent* attached to either position 2 or 3 of the phenanthridine ring (cf., the definitions of the present substituent groups R4 and R5 according to which either R4 represents ***-O-R41*** (and R5 is hydrogen or 1-4C-alkyl) or R5 represents ***-O-R51*** (and R4 is hydrogen or 1-4C-alkyl)).

They are furthermore novel over **D3** (published on ***11 March 2004***) on account of the present substituent group ***R7***:
The 6-phenyl group of the present 1,2,3,4,4a,10b-hexahydro-phenanthridin-(2- or 3-)-ol derivatives has to be substituted with a ***carboxamide*** group (cf., the substituent groups R6 and R7 of **D3** which may not represent a *carboxamide* group).

2. INVENTIVE STEP (Article 33(3) PCT):

The present application does not satisfy the criterion set forth in Article 33(3) PCT because the subject-matter of **claims 5-10** does not appear to involve an inventive step (Rule 65(1)(2) PCT):

2.1. It would appear that the present **claims 1-4** and **11-18** are **fully entitled** to the presently claimed **first** priority date of ***10.03.2004***.

Accordingly, the document **D4** - which is published on ***11.03.2004*** - may not be taken into account for the assessment of the question of inventive step.

The compounds of the present **claim 1 differ** from the compounds of **D1** and **D2** in that they have an *oxy substituent* attached to either position 2 or 3 of the phenanthridine ring (cf., the definitions of the present substituent groups R4 and R5 according to which either R4 represents ***-O-R41*** (and R5 is hydrogen or 1-4C-alkyl) or R5 represents ***-O-R51*** (and R4 is hydrogen or 1-4C-alkyl)).

In the light of this prior art the **problem** to be solved by the compounds of the present **claim 1** resides in the provision of <u>further</u> 6-phenyl-1,2,3,4,4a,10b-hexahydro-phenanthridine derivatives useful as *PDE4 inhibitors*.

The said problem has been **solved** by the compounds of the present **claim 1** (cf., the activity data (*PDE4 inhibition*) of table A on page 83 of the present description).

Given the fact that none of the prior art documents **D1** and **D2** suggests phenanthridine compounds with a 2- or 3- *oxy substituent*, it is considered that the present solution (i.e., the compounds of the present **claims 1-4**) may be regarded to be **non-obvious** in the sense of Article 33(3) PCT.

It is therefore considered that the subject-matter of the present **claims 1-4** and **11-18** involves an inventive step as set forth in the Article 33(3) PCT.

2.2. It would furthermore appear that the present **claims 5** and **6** are **only entitled** to the

present **second** priority date of ***17.12.2004***, and
the present **claims 7-9** and **10** (see, the last seven compounds) only to the present filing date of ***09.03.2005***.

Accordingly, the document **D3** - which is published on ***11.03.2004*** - is considered to represent state of the art in the sense of Article 33(3) PCT.

The compounds of the present **claims 5-10 differ** from the compounds of the prior art **D1** and **D2** essentially only in that they have an ***oxy*** *group* attached to either position 2 or 3 of the phenanthridine ring (cf., the definitions of the present substituent groups R4 and R5 according to which either R4 represents ***-O-R41*** (and R5 is hydrogen or 1-4C-alkyl) or R5 represents ***-O-R51*** (and R4 is hydrogen or 1-4C-alkyl)).
More specifically, **D1** discloses (cf., the example 20) the compound (+/-)-cis-4-(8,9-Dimethoxy-1,2,3,4,4a,10b-hexahydro-phenanthridin-6-yl)-*N-methyl*-benz*amide*.

Furthermore, the compounds of the present **claims 5-10 differ** from the compounds of **D3** essentially only in that the present 1,2,3,4,4a,10b-hexahydro-phenanthridin-*2-ol* derivatives have to have a ***carboxamide*** group (cf., the present substituent group -C(=O)-R7) attached to the 6-phenyl group (cf., e.g. the *alkoxycarbonyl* group C(=O)OR61 according to claim 1 of **D3**).
More specifically, **D3** discloses (cf., the example 8) the compound (+/-)-(2RS,4aRS,10bRS)-8,9-Dimethoxy-6-(4-*methoxycarbonyl*phenyl)-1,2,3,4,4a,10b-hexahydro-phenanthridin-*2-ol*).

In the light of this prior art the **problem** to be solved by the compounds of the present **claims 5-10** resides in the provision of <u>further</u> 6-phenyl-1,2,3,4,4a,10b-hexahydro-phenanthridine derivatives useful as *PDE4 inhibitors*.

The said problem has been **solved** by the compounds of the present **claims 5-10** (cf., the

activity data (*PDE4 inhibition*) of table A on page 83 of the present description).

Given the teaching of **D1** and **D3**, it is considered that the present solution does not appear to involve an inventive step for the following reasons:

1. It is known from **D1** that 6-(***carbamoyl***phenyl)-1,2,3,4,4a,10b-hexahydro-phenanthridine derivatives possess *PDE4 inhibitory* activity (see, for instance, the table A of **D1** according to which e.g.
the compound (+/-)-cis-4-(8,9-Dimethoxy-1,2,3,4,4a,10b-hexahydro-phenanthridin-6-yl)-***N-methyl***-benz***amide*** (compound 20) inhibits *PDE4*: -log IC_{50} = ***5.18*** .

2. It is furthermore known from **D3** that 6-(*alkoxycarbonyl*phenyl)-1,2,3,4,4a,10b-hexahydro-phenanthridin-***2-ol*** derivatives likewise possess *PDE4 inhibitory* activity (see, for instance, the table A of **D3** according to which e.g.
the compound (+/-)-(2RS,4aRS,10bRS)-8,9-Dimethoxy-6-(4-*methoxycarbonyl*phenyl)-1,2,3,4,4a,10b-hexahydro-phenanthridin-***2-ol*** (compound 8) inhibits *PDE4*:
-log IC_{50} = ***8.71*** .

3. It is also known from **D1** that **both**, i.e., 6-(***alkoxycarbonyl***phenyl)- **and** 6-(***carbamoyl***phenyl)-1,2,3,4,4a,10b-hexahydro-phenanthridine derivatives possess *PDE4 inhibitory* activity (see, for instance, the table A of **D1** according to which e.g.
the compound (+/-)-cis-4-(8,9-Dimethoxy-6-(4-***methoxycarbonyl***phenyl)-1,2,3,4,4a,10b-hexahydro-phenanthridine (compound 1) inhibits *PDE4*:
-log IC_{50} = ***7.39*** , and
the compound (+/-)-cis-4-(8,9-Dimethoxy-1,2,3,4,4a,10b-hexahydro-phenanthridin-6-yl)-***N-methyl***-benz***amide*** (compound 20) inhibits *PDE4*: -log IC_{50} = ***5.18*** .

4. It is further known from **D1** and **D3** that 6-(*alkoxycarbonyl*phenyl)-1,2,3,4,4a,10b-hexahydro-phenanthridine **as well as** 6-(*alkoxycarbonyl*phenyl)-1,2,3,4,4a,10b-hexahydro-phenanthridin-***2-ol*** derivatives possess *PDE4 inhibitory* activity (see, for instance, the table A of **D1** according to which e.g.
the compound (+/-)-cis-4-(8,9-Dimethoxy-6-(4-*methoxycarbonyl*phenyl)- 1,2,3,4,4a,10b-hexahydro-phenanthridine (compound 1) inhibits *PDE4*:

-log IC_{50} = ***7.39*** , and
the table A of **D3** according to which e.g.
the compound (+/-)-(2RS,4aRS,10bRS)-8,9-Dimethoxy-6-(4-*methoxycarbonyl*phenyl)-1,2,3,4,4a,10b-hexahydro-phenanthridin-***2-ol*** (compound 8) inhibits *PDE4*:
-log IC_{50} = ***8.71*** .

5. Accordingly, it would have been clear to the person skilled in the art that the accordingly modified compounds
(i) 20 of **D1** (i.e., 1,2,3,4,4a,10b-hexahydro-phenanthridin-***2-ol*** instead of the 1,2,3,4,4a,10b-hexahydro-phenanthridine), and
(ii) 8 of **D3** (i.e., 6-(4-(***N-methylaminocarbonyl***phenyl)-1,2,3,4,4a,10b-hexahydro-phenanthridin-*2-ol* instead of 6-(4-*methoxycarbonyl*phenyl)-1,2,3,4,4a,10b-hexahydro-phenanthridin-*2-ol*)
would display (some) *PDE4 inhibitory* activity.

It is therefore considered that - in the absence of any ***unexpected / surprising effect*** - the compounds of the present **claims 5-10** have to be regarded to be **obvious** in the light of the teaching of **D1** and **D3**.

3. INDUSTRIAL APPLICABILITY (Article 33(4) PCT):

The subject-matter of the present **claims 1-16** concerns chemical compounds, pharmaceutical compositions and the use of chemical compounds for the production of pharmaceutical compositions and is therefore considered to be industrial applicable in the sense of Article 33(4) PCT.